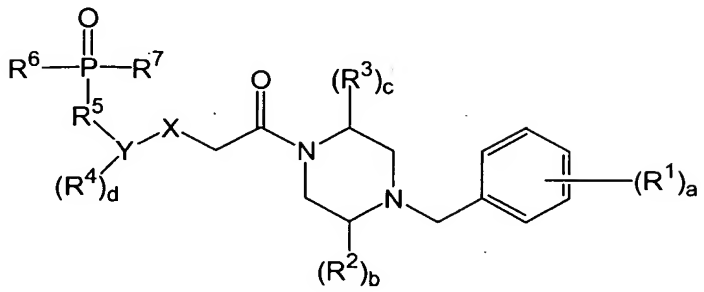
CLAIMS

1. A compound of the Formula I,



I

a prodrug thereof, or a pharmaceutically acceptable salt of the compound or theprodrug thereof; wherein,

a = 0, 1, 2, 3, 4 or 5;

b = 0, 1 or 2;

c = 0, 1 or 2;

d = 0, 1, 2, 3 or– 4;

X is O, S, CH_2 or NR^6;

Y is (C_6-C_{10})aryl or (C_2-C_9)heteroaryl;

each R^1 is independently: hydroxy, halo, (C_1-C_8)alkyl optionally substituted with 1 to 3 fluorine atoms, (C_1-C_8)alkoxy optionally substituted with 1-3 fluorine atoms, HO(C_1-C_8)alkyl-, cyano, amino, H_2N(C_1-C_8)alkyl-, carboxy, acyl, (C_1-C_8)alkyl(C=O)(C_1-C_8)alkyl-, H_2N(C=O)-, or H_2N(C=O)(C_1-C_8)alkyl-;

each R^2 and R^3 are independently: oxo, (C_1-C_8)alkyl optionally substituted with 1-3 fluorine atoms, (C_3-C_8)cycloalkyl-, (C_3-C_8)cycloalkyl-(C_1-C_8)alkyl-, (C_6-C_{10})aryl-, (C_6-C_{10})aryl(C_1-C_8)alkyl-, HO(C_1-C_8)alkyl-, (C_1-C_8)alkyl-O-(C_1-C_8)alkyl-, H_2N(C_1-C_8)alkyl-, (C_1-C_8)alkyl-NH-(C_1-C_8)alkyl-, [(C_1-C_8)alkyl]$_2$N-(C_1-C_8)alkyl-, (C_2-C_9)heterocyclyl(C_1-C_8)alkyl-, (C_1-C_8)alkyl(C=O)NH(C_1-C_8)alkyl-, (C_1-C_8)alkyl-O-(C=O) NH (C_1-C_8)alkyl-, H_2N(C=O)NH(C_1-C_8)alkyl-, (C_1-C_8)alkyl-SO_2-NH(C_1-C_8)alkyl-, (C_2-C_9)heteroaryl(C_1-C_8)alkyl-, H_2N(C=O), or H_2N(C=O)(C_1-C_8)alkyl-;

each R^4 is independently: HO-, halo-, NC-, HO(C=O)-, H_2N-, (C_1-C_8)alkylNH-, [(C_1-C_8)alkyl]$_2$N-, (C_1-C_8)alkyl-, optionally substituted with 1-3 fluorine atoms, (C_1-C_8)alkoxy optionally substituted with 1-3 fluorine atoms, HO(C_1-C_8)alkyl-, (C_1-C_8)alkyl-

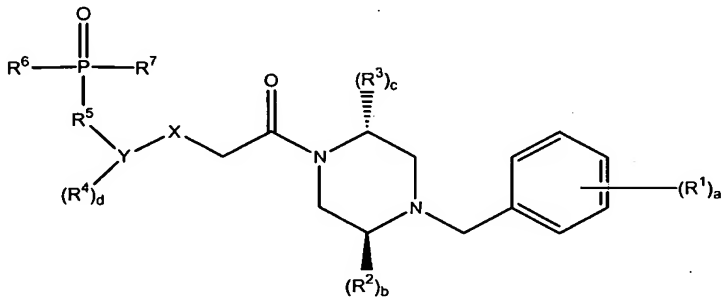
O-(C_1-C_8)alkyl-, H_2N(C_1-C_8)alkyl--, (C_1-C_8)alkylNH(C_1-C_8)alkyl-, [(C_1-C_8)alkyl]$_2$N(C_1-C_8)alkyl-; (C_1-C_8)alkyl(C=O)-, (C_1-C_8)alkyl(C=O)(C_1-C_8)alkyl-, (C_6-C_{10})aryl-, (C_2-C_9)heteroaryl-, (C_6-C_{10})aryloxy-, H_2N(C=O)-, H_2N(C=O)(C_1-C_8)alkyl-, (C_1-C_8)alkylNH(C=O)-, (C_1-C_8)alkyl-NH(C=O)(C_1-C_8)alkyl-, [(C_1-C_8)alkyl]$_2$N(C=O)-, [(C_1-C_8)alkyl]$_2$N(C=O)(C_1-C_8)alkyl-, (C_3-C_8)cycloalkyl-, (C_1-C_8)alkylSO$_2$-, NC(C_1-C_8)alkyl-, (C_1-C_8)alkyl(C=O)NH-, H_2N(C=O)NH- or H_2N(C=O)NH(C_1-C_8)alkyl-;

R^5 is a bond or a (C_1-C_8)alkyl-;

R^6 is independently: hydroxy, amine or (C_1-C_8)alkyl-NH-; and

R^7 is independently: hydrogen, hydroxyl, (C_1-C_8)alkoxy- or (C_1-C_8)alkyl-.

2. A compound according to Claim 1, wherein the compound of Formula I has the stereochemistry showin in Formula Ia



Ia

wherein a, b, c, X, Y, R^1, R^2, R^3, R^4, R^5, R^6 and $R^7$are as described above.

3. A compound according to Claim 1, wherein R^1 is: hydroxy, halo, cyano, (C_1-C_8)alkyl- optionally substituted with 1-3 fluorine atoms, or (C_1-C_8)alkoxy optionally substituted with 1-3 fluorine atoms.

4. A compound according to Claim 1, wherein R^4 is hydroxyl, cyano, (C_1-C_8)alkyl- optionally substituted with 1-3 fluorine atoms, (C_1-C_8)alkoxy optionally substituted with 1-3 fluorine atoms, (C_1-C_8)alkyl(C=O)- or halo-.

5. A compound according to Claim 1, wherein X is O and R^5 is (C_1-C_3)alkyl-.

6. A compound according to Claim 1, wherein R^2 and R^3 are each independently: (C_1-C_8)alkyl-, optionally substituted with 1-3 fluorine atoms; (C_3-C_8)cycloalkyl-; (C_3-C_8)cycloalkyl-(C_1-C_8)alkyl-; (C_6-C_{10})aryl-; (C_6-C_{10})aryl(C_1-C_8)alkyl-; HO(C_1-C_8)alkyl-; H_2N(C_1-C_8)alkyl-; (C_2-C_9)heterocyclyl(C_1-C_8)alkyl-; (C_1-C_8)alkyl-O-(C=O)NH(C_1-C_8)alkyl-; H_2N(C=O)NH(C_1-C_8)alkyl-; (C_1-C_8)alkyl-SO$_2$NH(C_1-C_8)alkyl-; (C_2-C_9)heteroaryl(C_1-C_8)alkyl-; H_2N(C=O)- or H_2N(C=O)(C_1-C_8)alkyl-.

7. A compound according to Claim 6, wherein R^2 and R^3 are each independently (C_1-C_8)alkyl-, optionally substituted with 1-3 fluorine atoms; or (C_3-C_8)cycloalkyl-.

8. A compound according to Claim 1, wherein

R^1 is: hydroxy, halo, cynao, (C_1-C_8)alkyl optionally substituted with 1-3 fluorine atoms, or (C_1-C_8)alkoxy- optionally substituted with 1-3 fluorine atoms;

R^2 and R^3 are each independently (C_1-C_8)alkyl, optionally substituted with 1-3 fluorine atoms; or (C_3-C_8)cycloalkyl-;

R^4 is HO-, NC-, (C_1-C_8)alkyl- optionally substituted with 1-3 fluorine atoms, (C_1-C_8)alkoxy optionally substituted with 1-3 fluorine atoms, (C_1-C_8)alkyl(C=O)- or halo-;

X is O; and

R^5 is (C_1-C_3)alkyl-.

9. A compound according to Claim 1, wherein the compound is:

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid;

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid;

(5-Chloro-2-{2-[(2R)-2-ethyl-4-(4-fluoro-benzyl)-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid;

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid;

(5- Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid;

[2-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-ethyl]-phosphonic acid;

[2-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-ethyl]-phosphonic acid;

[2-(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-ethyl]-phosphonic acid;

[2-(5- Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-ethyl]-phosphonic acid;

(5-Chloro-2-{2-[4-(4-chloro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid;

(5-Chloro-2-{2-[4-(4-chloro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid;

(5-Bromo-2-{2-[4-(4-chloro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid;

(5- Bromo -2-{2-[4-(4-chloro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid;

(5-Chloro-2-{2-[4-(3,4-difluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid;

(5-Chloro-2-{2-[4-(3,4-difluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid;

(5-Bromo-2-{2-[4-(3,4-difluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid;

(5-Bromo-2-{2-[4-(3,4-difluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid;

[2-(5-Chloro-2-{2-[4-(4-chloro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-ethyl]-phosphonic acid;

[2-(5-Bromo-2-{2-[4-(4-chloro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-ethyl]-phosphonic acid;

[2-(5-Chloro-2-{2-[4-(3,4-difluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-ethyl]-phosphonic acid;

[2-(5-Bromo-2-{2-[4-(3,4-difluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-ethyl]-phosphonic acid;

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-pyridin-3-ylmethyl)-phosphonic acid;

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-pyridin-3-ylmethyl)-phosphonic acid;

[2-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-pyridin-3-yl)-ethyl]-phosphonic acid;

[2-(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-pyridin-3-yl)-ethyl]-phosphonic acid;

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphinic acid;

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-methyl-phosphinic acid;

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-ethyl-phosphinic acid;

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid monomethyl ester;

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid monoethyl ester;

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-ethyl- phosphonamidic acid;

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)- phosphonamidic acid monomethyl ester; or

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonamidic acid monoethyl ester.

10. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 1, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, and a pharmaceutically acceptable diluent or carrier.

11. A therapeutic method of inhibiting MIP-1α and/or RANTES from binding to the receptor CCR1 in a mammal, including a human, comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound according to Claim 1.

12. A method of treating a condition mediated by inhibiting MIP-1α and/or RANTES from binding to the receptor CCR1, comprising admininistering to a mammal in need of such treatment a therapeutically effective amount of a compound according to Claim 1.

13. The method according to Claim 12, wherein the condition treated or prevented is selected from autoimmune diseases; fibrosis; allergic conditions; acute and chronic lung inflammation; atherosclerosis; Alzheimer's disease; vascular inflammation resulting from tissue transplant or during restenosis; acute and chronic inflammatory conditions; acute or chronic transplant rejection; HIV infectivity; granulomatous diseases; conditions associated with leptin production; sequelae associated with cancer; tissue damage caused by inflammation induced by infectious agents; viral inflammation of the lung or liver; gastrointestinal inflammation;inflammation resulting from bacterial meningitis, HIV-1, HIV-2, HIV-3, cytomegalovirus, adenoviruses, Herpes viruses, fungal meningitis, lyme disease, or

malaria; rheumatoid arthritis; Takayasu arthritis; psoriatic arthritis; ankylosing spondylitis; type I diabetes (recent onset); lupus; inflammatory bowel disease; Chrohn's disease; optic neuritis; psoriasis; multiple sclerosis; polymyalgia rheumatica; uveitis; thyroiditis; vasculitis; pulmonary fibrosis; idiopathic pulmonary fibrosis; interstitial pulmonary fibrosis; fibrosis associated with end-stage renal disease; fibrosis caused by radiation; tubulointerstitial fibrosis; subepithelial fibrosis; scleroderma; progressive systemic sclerosis; hepatic fibrosis; primary and secondary biliary cirrhosis; asthma; contact dermatitis; atopic dermatitis; chronic bronchitis; chronic obstructive pulmonary disease; adult Respiratory Distress Syndrome; Respiratory Distress Syndrome of infancy; immune complex alveolitis; restenosis following angioplasty and/or stent insertion; synovial inflammation caused by arthroscopy, hyperuremia, or trauma; osteoarthritis; ischemia reperfusion injury; glomerulonephritis; nasal polyosis; enteritis; Behcet's disease; preeclampsia; oral lichen planus; Guillian-Barre syndrome; xeno-transplantation rejection; sarcoidosis; leprosy; tuberculosis; obesity; cachexia; anorexia; type II diabetes; hyperlipidemia; hypergonadism; sequelae associated with multiple myeloma; viral-induced encephalomyelitis or demyelination; viral inflammation of the lung or liver caused by influenza or hepatitis; and *H. pylori* infection.

14. A therapeutic method of treating a condition mediated by inhibiting the production of metalloproteinases and cytokines at inflammatory sites comprising administering to a mammal, including a human, in need of such treatment a therapeutically effective a mount of a compound according to Claim 1.

15. The method according to Claim 14, wherein the condition treated is joint tissue damage, hyperplasia, pannus formation, bone resorption, hepatic failure, Kawasaki syndrome, myocardial infarction, acute liver failure, septic shock; congestive heart failure, pulmonary emphysema or dyspnea associated therewith.